Clopidogrel in the Management of Acute Coronary Syndromes

Indications, Results, Obstacles

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Abstract: Atherothrombosis is the underlying pathology of the acute coronary syndromes (ACS), in which platelet activation plays a key role. Therefore, antiplatelet therapy is an essential component of guideline-recommended ACS management. Considerable evidence clearly demonstrates the benefits of the antiplatelet agent clopidogrel in reducing mortality, decreasing recurrent cardiovascular events, and increasing arterial patency in ACS patients. Despite this evidence, data from patient registries and clinical initiatives such as CRUSADE (Can Rapid stratification of Unstable angina Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines) and GRACE (Global Registry of Acute Coronary Events) indicate that clopidogrel is underused in patients with ACS. This is especially true for patients receiving conservative medical management, many of whom have significant risk for recurrent ischemic events. The purpose of this review is to compare "real-life" clopidogrel therapy with evidence-based guidelines, and to highlight clinical factors that drive clopidogrel implementation or provide barriers to its use in ACS patients.

Key Words: acute coronary syndrome, antiplatelet therapy, interventional management, medical management

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The acute coronary syndromes (ACS) encompass acute myocardial infarction (MI) and unstable angina (UA). Based on electrocardiographic features and cardiac injury markers, approximately 30% to 45% of ACS patients have ST-elevation MI (STEMI) and 55% to 70% have either UA or non-ST-elevation MI (NSTEMI).[1] STEMI patients have the highest risk for mortality during the critical period immediately after symptom onset and require antiplatelet therapy and urgent treatment with either fibrinolytic or mechanical revascularization.[2] Two major treatment strategies are recommended for treating UA/NSTEMI patients: an early invasive approach or conservative medical management.[3] The invasive strategy is recommended for UA/NSTEMI patients at high risk of ischemic complications and includes coronary angiography and revascularization, generally performed within 4 to 24 hours of admission, in addition to unfractionated or low molecular weight heparin and antiplatelet therapy with aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors. The majority of UA/NSTEMI patients are managed by the early invasive strategy. The conservative approach is recommended for patients without a high risk of ischemic complications and comprises antiplatelet therapy with aspirin, clopidogrel, and eptifibatide or tirofiban in addition to heparin. Comprehensive ACS therapy also includes anti-ischemic drugs and other agents indicated by patients' clinical indications.

As can be seen, clopidogrel is a basic component of antiplatelet therapy for both STEMI and UA/STEMI patients. It is the purpose of this review to highlight the role of clopidogrel in ACS management, emphasizing recent findings of clinical practice from the CRUSADE (Can Rapid stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association [ACC/AHA] guidelines) initiative.[4] Factors that may serve as barriers to clopidogrel initiation will also be addressed.

Clopidogrel Therapy for STEMI

Data from 2 clinical trials have expanded clopidogrel's role in STEMI from ancillary therapy in patients undergoing percutaneous coronary intervention (PCI) to a key component of standard fibrinolytic regimens and early treatment plans.[2] In the CLopidogrel as Adjunctive ReperfusIon TherapY—Thrombolysis In Myocardial Infarction study 28 (CLARITY-TIMI 28), 3491 patients with STEMI were randomized to 75 mg/d clopidogrel (after a loading dose of 300 mg) or placebo in addition to fibrinolytic therapy, aspirin, and, when relevant, heparin[5]; all patients were scheduled to undergo angiography 48 to 192 hours after starting study treatment. Clopidogrel was associated with a 36% reduction (95% CI: 24%–47%; $P < 0.001$) in the primary study end point (angiographic evidence of TIMI grade 0–1 occlusion of an infarct-related artery or death or recurrent MI before angiography). By day 30, clopidogrel reduced the odds of the composite end point (cardiovascular death, recurrent MI, or recurrent ischemia necessitating urgent revascularization) by 20% (95% CI: 3%–35%; $P = 0.03$) compared with placebo (Fig. 1).[5] There were no significant excesses of major or minor bleeding during the 30-day trial.

In the ClOpidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2), nearly 46,000 patients with suspected acute MI who were not scheduled for PCI were enrolled within 24 hours of symptom onset.[6] All patients received aspirin and were randomized to either clopidogrel 75 mg/d or placebo for a mean period of 16 days. Fibrinolytic and anticoagulant therapies were used in ~50% and ~75% of patients, respectively. The rate of the composite end point (death, reinfarction, or stroke) was significantly lower in the clopidogrel patients (9.2% vs. 10.1%; relative risk [RR] reduction 9%; 95% CI: 3%–14%; $P = 0.002$), as was in-hospital mortality (RR reduction 7%; 95% CI: 1%–13%; $P = 0.03$). The proportional reduction in the composite end point was similar in patients who did and did not receive fibrinolytic therapy (11% vs. 7%). Dual antiplatelet therapy was associated with an excess of 0.4 ($P = 0.59$) major and 4.7 ($P = 0.005$) minor bleeding episodes per 1000 patients. These findings suggest that treating 1000 STEMI patients with 75 mg/d clopidogrel for 2 weeks could prevent ~10 major vascular events, or for every 1 million STEMI patients given clopidogrel for approximately 14 days, 5000 deaths and 5000 nonfatal events could be avoided at a cost of 400 major bleeds.[6]

Prospective registry data of 292 patients who received primary PCI also support the benefit of clopidogrel pretreatment in STEMI.[7] Upon multivariable regression analysis, clopidogrel pre-

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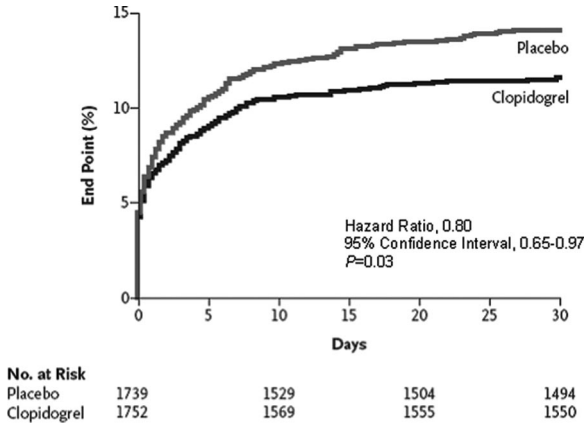

FIGURE 1. Efficacy of clopidogrel in ST-Elevation Myocardial Infarction (STEMI). Patients in the CLARITY-TIMI 28 trial. 3,491 patients who presented within 12 hours after STEMI onset were enrolled in the study to compare clopidogrel (300 mg loading dose followed by 75 mg once daily) with placebo. CLARITY-TIMI 28, CLopidogrel as Adjunctive Reperfuslon TherapY—Thrombolysis In Myocardial Infarction study 28. Reproduced with permission from Sabatine et al. *New Engl J Med.* 2005;352:1179–1189.[5] Copyright © 2005 Massachusetts Medical Society. All rights reserved.

treatment was associated with more than a 2-fold increase in the proportion of patients with TIMI myocardial perfusion grade 3 after PCI (OR: 2.2; 95% CI: 1.2–3.9; $P = 0.01$). Clopidogrel pretreatment was also associated with lower rates of reinfarction at 30 days (0% vs. 3.2% of patients who did not receive pretreatment; $P = 0.04$) and stent thrombosis at 6 months (0% vs. 3.9%; $P = 0.02$).[7]

Clopidogrel Therapy for UA/NSTEMI

The efficacy of dual antiplatelet therapy with aspirin and clopidogrel in UA/NSTEMI patients was first demonstrated in the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial of >12,000 patients.[8–10] Patients were randomized to clopidogrel 75 mg/d (after a loading dose of 300 mg) or placebo for a mean duration of 9 months in addition to aspirin. The primary outcome of cardiovascular death, nonfatal MI, or stroke occurred in significantly fewer clopidogrel than placebo recipients (RR: 0.80; 95% CI: 0.72–0.90).[9] Further, the onset of these salutary effects was seen as early as 2 hours after therapy initiation (Fig. 2).[11] The benefit of dual therapy was observed in all patients, regardless of their initial risk, and was similar in patients managed medically or by revascularization.[8] Clopidogrel was associated with an increased risk of major bleeding (RR: 1.38; 95% CI: 1.13–1.67; $P < 0.001$).[10] Thus, regardless of conservative or invasive management, early and consistent clinical benefits are associated with dual antiplatelet therapy in UA/NSTEMI patients.

Clopidogrel Use as Observed in CRUSADE

CRUSADE is a national quality and educational initiative designed to improve guideline adherence in UA/NSTEMI patient management.[4] Data from CRUSADE shows that increased adherence to guideline-recommended therapy significantly improves outcomes in UA/NSTEMI patients, as indicated by a 10% decrease in mortality for each 10% increase in guidelines adherence (Fig. 3).[12]

Findings from CRUSADE demonstrated that clopidogrel is underutilized in both acute and discharge settings and across many subsets of patients, including the elderly,[13] women,[14] African Americans,[15] Hispanics,[16] those classified as high risk,[17] and those with chronic kidney disease[18] or congestive heart failure.[19] Thus, clopidogrel was used in only 60% of eligible patients in the acute setting and approximately 75% at discharge, compared with the nearly 100% guideline-compliant use of aspirin in both the acute and discharge settings for the same period.[13]

Additional findings from CRUSADE indicate that underuse of clopidogrel, both acutely and at discharge, is most frequent in the medically managed group. In one analysis, its use was 51% in patients managed invasively and 26% in those managed medically.[20] Further, of >65,000 patients admitted to 462 hospitals participating

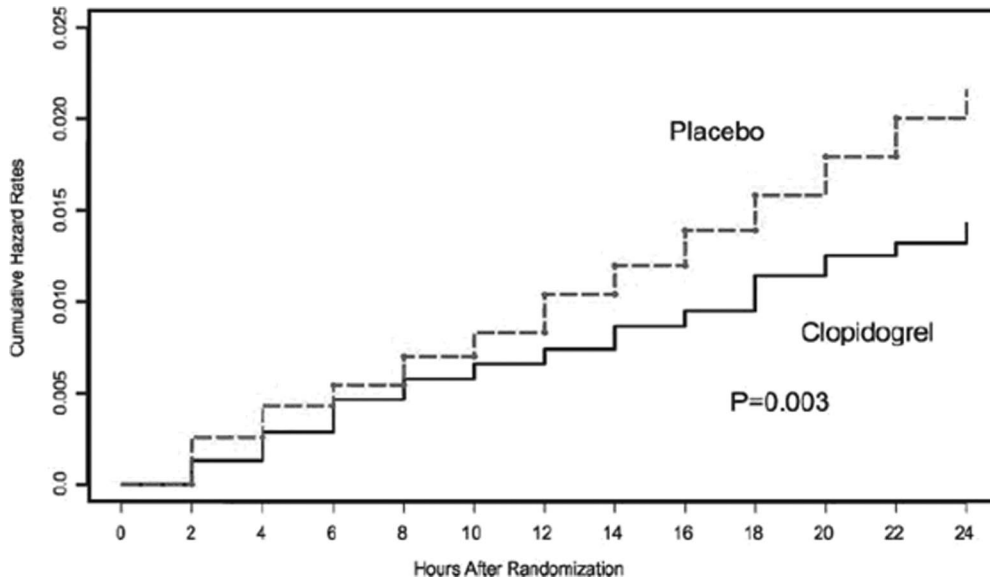

FIGURE 2. Cumulative hazard ratio of the primary end point within the first 24 hours after randomization in the CURE trial. The primary end point is a composite of cardiovascular death or nonfatal myocardial infarction or stroke. CURE, Clopidogrel in Unstable angina to prevent Recurrent Events. Reproduced with permission from Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidorel in patients with acute coronary syndromes. *Circulation.* 2003;107(7):966–972.[11]

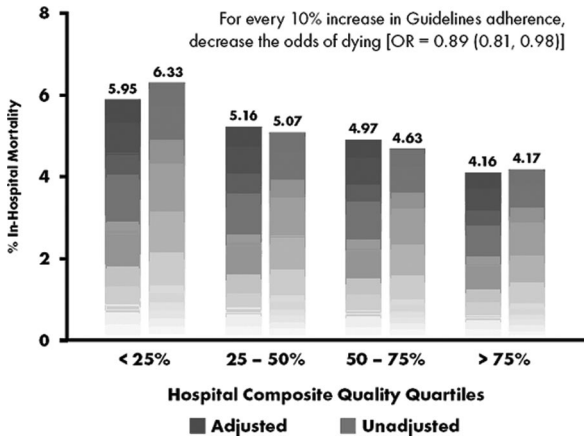

FIGURE 3. Relationship between overall composite quality and in-hospital mortality. Overall composite quality of hospitals is based on adherence scores and calculated as the number of guideline-compliant care instances out of the total number of opportunities. 64,775 patients were included from a total of 403 US hospitals that submitted >40 cases. Odds ratios were adjusted for patient demographics, presenting cardiac symptoms, and medical history. OR indicates odds ratio. Reproduced with permission from Peterson et al. *JAMA.* 2006;295: 1912–1920.[12]

in the CRUSADE initiative, <50% of eligible patients who did not receive PCI were prescribed clopidogrel at discharge, compared with 90% to 95% of those who did receive PCI.[21] Additional data do suggest that, although medically managed patients remain undertreated with clopidogrel, its use is increasing. From 2002 to 2005, acute therapy with clopidogrel in medically managed patients increased from 23% to 43%, whereas its prescription at discharge increased from 28% to 53%.[22] During this interval, acute aspirin use increased from 87% to 93% and from 82% to 90% at discharge.

Paradoxically, data from CRUSADE shows that patients stratified as high risk received clopidogrel within 24 hours of presentation less often than patients classified as low risk (36.2% vs. 46.1%).[17] These data seemingly support the underuse of clopidogrel in medically managed patients, as high-risk patients also underwent fewer invasive cardiac procedures than low-risk patients.[17]

Clopidogrel Use as Observed in Other Patient Registries

Data from several patient registries show that despite its well-documented benefits, clopidogrel is spontaneously discontinued by up to 18% of patients.[23] Premature discontinuation of clopidogrel among drug-eluting stent (DES) recipients is particularly problematic as it has been associated with late stent thrombosis and poor clinical outcomes.[24–26] These findings led to a recommendation stressing the importance of maintaining 12 months of dual antiplatelet therapy in patients with DES,[27] and the inclusion of this recommendation in the 2007 focused update of the evidence-based guidelines for PCI.[28]

Although available evidence supports upstream initiation of clopidogrel in STEMI patients, recent data from the ACTION Registry, a national quality improvement initiative for all ACS patients, shows that clopidogrel utilization remains lower than that of aspirin. In 11,854 STEMI patients, utilization of clopidogrel in the acute setting was 84%, compared with 98% for aspirin, whereas rates at discharge were 99% and 90%, respectively.[29] Although this finding is encouraging compared with earlier data from the Global Registry of Acute Coronary Events (GRACE), in which only 55% of patients received thienopyridines in the acute setting,[30] the need for continuing improvement is apparent.

Similar to what was shown for UA/NSTEMI patients in CRUSADE, high-risk patients in GRACE received clopidogrel less often than those who were low risk.[30] Specifically, high-risk patients were 34% less likely to receive clopidogrel (95% CI: 31%–37%; $P < 0.0001$) within 24 hours of symptom onset.

Variability in Response to Clopidogrel

Recent studies have shown considerable variability in response to clopidogrel.[31–33] Patients whose platelets display the lowest responsiveness to antiplatelet therapy upon ex vivo testing are often referred to as aspirin or clopidogrel "resistant."[34] However, this term is controversial and may be misleading as there is no standard definition of resistance or its measurement.[34,35] Furthermore, patients classified as resistant by one test may show responsiveness by another.[36,37] Emerging evidence suggests that the *CYP2C19*2* allele may contribute to decreased platelet responsiveness after clopidogrel administration.[38–40] The observation that patients whose platelets are least responsive to antiplatelet therapy may have an increased incidence of adverse cardiovascular events[41–47] has contributed to the development of platelet reactivity-guided antiplatelet therapy,[45,47a] as well as newer antiplatelet agents that more intensely inhibit platelet activity and appear to be associated with less resistance.[40,48–51]

Of these novel antiplatelet agents, most clinical experience pertains to the thienopyridine prasugrel, which was recently approved for marketing by the European Medicines Agency.[52] In the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), which compared, on a background of aspirin, the safety and efficacy of prasugrel with clopidogrel in 13,608 ACS patients with known coronary anatomy, prasugrel was associated with a 19% reduction in the risk of the primary end point of cardiovascular death, MI, and stroke (HR: 0.81; 95% CI: 0.73–0.90; $P < 0.001$).[53] Compared with clopidogrel, prasugrel improved outcomes both early (randomization to 3 days) and late (day 3 to end of trial).[54] In prespecified subgroup analyses, patients with diabetes mellitus[55] and those who received stents[56] had improved outcomes with prasugrel. Although prasugrel clearly decreased the risk of cardiovascular events, it was associated with a significant increase in the risk of bleeding. In the overall population, prasugrel recipients had a 32% increase in major bleeding risk (HR: 1.32; 95% CI: 1.03–1.68; $P = 0.03$) and a 52% increase in life-threatening bleeding risk (HR: 1.52; 95% CI: 1.08–2.13; $P = 0.01$).[53] Bleeding risk was particularly increased in patients with a history of stroke or transient ischemic attack (TIA), age ≥75 years, and weight <60 kg. Excess bleeding associated with prasugrel occurred ≥3 days after therapy initiation (ie, in the maintenance phase).[54] Notably, patients with diabetes mellitus did not have a significantly increased risk of bleeding when taking prasugrel.[55] Calculation of net clinical benefit (ie, cardiovascular death, MI, stroke, or major bleeding) showed prasugrel to be superior to clopidogrel in patients without a history of stroke or TIA; patients with age <75 years, body weight ≥60 kg, and no history of stroke; patients with diabetes mellitus; and DES recipients (Table 1).[53,55,56] In contrast, prasugrel was associated with net clinical harm in patients with a history of stroke or TIA and a neutral effect (ie, no significant net harm or benefit) in patients with age ≥75 years, weight <60 kg, or history of stroke or TIA; no diabetes mellitus; or bare-metal stent recipients.[53,55,56] These data suggest that although more potent antiplatelet agents are beneficial for certain patient populations, particularly those with diabetes mellitus, or who are recipients of DES, they also suggest that the

TABLE 1. Net Clinical Effect for Prasugrel in Relation to Clopidogrel in TRITON-TIMI 38. Net Clinical Effect Included Cardiovascular Death, MI, Stroke, and Non-CABG-Related Major Bleeding

Patient Population	Prasugrel (%)	Clopidogrel (%)	Hazard Ratio (95% CI)	*P*
History of stroke or TIA[53]	23.0	16.0	1.54 (1.02–2.32)	0.04
No history of stroke or TIA[53]	11.8	13.8	0.84 (0.76–0.93)	<0.001
Age ≥75 yr, body weight <60 kg, or history of stroke or TIA[53]	20.2	19.0	1.07 (0.90–1.28)	0.43
Age <75 yr, body weight ≥60 kg, and no history of stroke or TIA[53]	10.2	12.5	0.80 (0.71–0.89)	<0.001
No history of diabetes mellitus[55]	11.5	12.3	0.92 (0.82–1.03)	0.16
History of diabetes mellitus[55]	14.6	19.2	0.74 (0.62–0.89)	0.001
Bare-metal stent recipients[56]	12	14	0.88 (0.77–1.01)	0.07
Drug-eluting stent recipients[56]	11	13	0.84 (0.72–0.98)	0.025

TRITON-TIMI 38 indicates TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN-Thrombolysis in Myocardial Infarction 38; CABG, coronary artery bypass grafting; CI, confidence interval; TIA, transient ischemic attack.

reduction of cardiovascular events is offset by major bleeding in other patient groups, including those with a history of stroke or TIA.

Barriers to Dual Antiplatelet Therapy

To optimize use of dual antiplatelet therapy with aspirin and clopidogrel, it is necessary to identify barriers to its initiation. A critical barrier in any patient population is evidence of increased bleeding risk. Although the addition of clopidogrel to aspirin resulted in numerically, though not necessarily statistically significantly, higher rates of bleeding in the CURE,[10] COMMIT,[6] and CLARITY[5] trials, a recent meta-analysis of these trials showed that the risk of major bleeding was not significantly increased by clopidogrel addition (OR: 1.31; 95% CI: 0.88–1.94).[57] Similar to results from several other meta-analyses,[58–60] analysis of CURE data showed that higher doses of aspirin increased the incidence of major and life-threatening bleeding without increasing therapeutic efficacy in both aspirin plus placebo and aspirin plus clopidogrel recipients.[61] In fact, the unadjusted rates of both major and life-threatening bleeding in patients receiving ≥200 mg/d of aspirin monotherapy exceeded the bleeding incidence of patients on dual therapy with ≤100 mg/d aspirin and 75 mg/d clopidogrel (3.7% vs. 3.0% for major and 2.4% vs. 1.8% for life-threatening bleeding).[61] Thus, current data suggest that although dual therapy with aspirin and clopidogrel may increase major bleeding risk in ACS patients, this risk can be mitigated by using aspirin doses ≤100 mg/d. The hypothesis that 75 to 100 mg/d aspirin causes less bleeding than 300 to 325 mg/d aspirin in ACS patients also receiving clopidogrel is currently being evaluated in the Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS 7 (CURRENT-OASIS 7) randomized clinical trial.[62]

A related barrier to initiating clopidogrel in ACS patients is the concern of excess bleeding if a patient should require coronary artery bypass grafting (CABG). In the subset of patients who underwent CABG in CURE, clopidogrel was associated with a nonsignificant excess of approximately 2 major and 1 life-threatening bleeds per 100 patients treated, but these excesses applied only to patients who continued clopidogrel within the 5 days before CABG.[8] Similarly, several prospective and retrospective studies have reported an increased risk of bleeding in patients who received clopidogrel within 4 to 7 days of CABG.[63–68] Although a clopidogrel washout period decreases bleeding risk, it is associated with an ~1% increase in reinfarction,[67,69] and increased costs because of prolonged hospital stay.[70] The ACC/AHA guidelines for both UA/NSTEMI and STEMI recommend clopidogrel cessation 5 to 7 days before CABG, unless the need for revascularization outweighs the risk of bleeding.[2,3]

The recommendation to withhold clopidogrel 5 to 7 days before CABG leads many physicians to delay clopidogrel administration until after coronary angiography, which is a determinant of the need for CABG. However, this practice may be detrimental to most of ACS patients. For example, in GRACE, only 7% of NSTEMI and 4% of STEMI patients underwent CABG.[30] Similarly, only 12% of patients in the CRUSADE cohort were referred for CABG.[13] Further, emergency CABG (within 12 hours of symptom onset, or as rescue after failed PCI) is necessary in only 1% to 3% of cases.[71,72] Therefore, because only a small proportion of patients receive CABG, the risk of bleeding in this group may not provide sufficient reason to withhold guideline-recommended upstream initiation of clopidogrel plus aspirin in ACS patients before angiography.

The cost of clopidogrel, approximately $3 to $4/d, is also a limiting factor to its use.[27,73] However, despite its expense, clopidogrel therapy has been shown to be cost-effective for ACS patients over the long-term. Meta-analyses of available pharmacoeconomic studies of clopidogrel suggest that dual antiplatelet therapy with clopidogrel and aspirin is cost-effective when used for up to 12 months in ACS patients and those undergoing PCI.[74,75]

CONCLUSIONS

A large body of evidence suggests that compared with aspirin alone, the addition of clopidogrel decreases the risk of death, recurrent MI, stroke, and the need for target vessel revascularization in ACS patients, although it does increase the risk of bleeding. Data from CRUSADE, GRACE, and ACTION show that despite its benefits, clopidogrel is underused in ACS patients, particularly those managed medically. Factors identified as barriers to clopidogrel initiation include an increased risk of bleeding, particularly if a patient should require CABG, response variability, and cost. However, if clopidogrel is routinely withheld as early treatment because of concern for increased bleeding and the modest possibility that a patient may require CABG, a considerable number of ACS patients will fail to receive its benefits. Furthermore, although up-front costs associated with clopidogrel are high, it is cost-effective in the long-term because of its beneficial effect on the risk of future adverse cardiovascular events. Although ongoing studies with novel antiplatelet agents may modify the role of clopidogrel in the future

management of ACS, clopidogrel is currently guideline-recommended antiplatelet therapy for all ACS patients and should be used accordingly.

DISCLOSURES

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